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**Wyeth**

March 11, 2004

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

**RE: Docket No. 2004N-0033; Factor VIII Inhibitor Workshop**

Dear Sir or Madam:

Reference is made to the October 20, 2003 Federal Register Notice (68 FR 59942) which announced an FDA sponsored public workshop entitled "Factor VIII Inhibitors". Additional reference is made to the Agency's February 11, 2004 announcement to stakeholders of the availability of Federal Docket number 2004N-0033 assigned to receive submissions of comments, critiques, or new information regarding topics covered at the November 21, 2003 Factor VIII Inhibitor Workshop.

As follow-up to the workshop, Wyeth would like to provide comments on proposals discussed at the meeting. Wyeth has prepared comments that reflect our analysis of the impact of these proposals or recommendations on the clinical development and regulatory approval of rFVIII products. Feedback is provided on assay development, pharmacokinetic (PK) trials, and proposals for safety endpoints for clinical studies of previously treated patients (PTPs) with hemophilia A.

Wyeth believes that clinical interpretation of inhibitor development should be central to future guidance for clinical trials. Wyeth does not agree with the recommendation by FDA to establish a statistical standard for clinical trials of new FVIII products wherein the upper bound confidence interval for the product inhibitor incidence rate must be below 6.8%. This approach relies on an estimate of the true rate of inhibitor incidence to be less than or equal to 1%, which during the workshop clinical experts considered was too low. In response Wyeth has recommended an alternate statistical approach, based on Bayesian analysis, which demonstrates the ability to discriminate between approved products and an increased inhibitor rate associated with a product related manufacturing change.

Per the Agency's request in the aforementioned February 11 announcement, Wyeth is re-submitting these comments to the Federal Docket for general consideration.

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Please contact the undersigned at (617) 665-8618 or Joyce Schwenk at (484) 865-5938 if there are any questions regarding the contents of this submission.

Sincerely,



Robin Evers  
Senior Director, Worldwide Regulatory Affairs

**Response to 21 Nov 2003 Inhibitor Forum**

**WYETH PHARMACEUTICALS**

**RESPONSE TO 21 NOV 2003 INHIBITOR FORUM**

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### **WYETH PHARMACEUTICALS**

#### **RESPONSE TO 21 NOV 2003 INHIBITOR FORUM**

##### **1. Introduction**

Wyeth Pharmaceuticals is a research-based pharmaceutical company, involved in the research and development, manufacture, and marketing of recombinant Factor VIII (rFVIII). Wyeth appreciates the opportunity to participate in the FDA initiative for public consultation on inhibitor development. The following comments reflect our analysis of the impact of specific proposals or recommendations on the clinical development and regulatory approval of FVIII products. Feedback is provided on assay development, pharmacokinetic (PK) trials, and proposals for safety endpoints for clinical studies of previously treated patients (PTPs) with hemophilia A.

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### **2. Assays**

Wyeth recognizes the importance of assay performance for the laboratory detection of inhibitor development, which was discussed during the inhibitor workshop. Wyeth believes that the interpretation of inhibitor assay results must be made in the context of clinically relevant safety data in clinical trials.

It is well recognized that inhibitor assays are characterized by significant inter-assay variability and may not detect every clinically significant inhibitor. These issues, which were summarized and extensively discussed during the meeting, are problematic for the reliable identification of patients who meet enrollment criteria in clinical studies of FVIII products and for the interpretation of de novo inhibitor development data in these studies. For example, clinical PTP study protocols usually require exclusion of patients with a history of FVIII inhibitors and define a patient as having developed an inhibitor if even a slight positive titer result is observed. Assay sensitivity and variability further confound the proposal that stopping rules be based only on incidence of de novo inhibitor development without regard to the magnitude or clinical effects of the inhibitor response. The outcome of the study would be highly dependent upon the differences in performance characteristics of the assays performed to detect a possible inhibitor by the study laboratory and those performed throughout the patient's lifetime.

These assay problems might be addressed in part by adoption of more sensitive or harmonized assays throughout the hemophilia testing laboratory world. A number of approaches are currently at the development stage and would require extensive validation prior to required implementation in future studies.

Data presented verified a high level of inter-laboratory variability and suggested that the adoption of an international reference standard might mitigate this problem. While this recommendation has merit, the selection of an appropriate inhibitor reference standard for quantification is based on the presumption that the reference and test samples will have parallel "dose"-response relationships. This will only occur in a "like vs. like" situation in which the reference and test samples all contain inhibitor antibodies with the same composition and properties, albeit at different concentrations. However, the composition of inhibitor test samples will undoubtedly vary depending on the stage in the immune response at which they are collected from a patient and on the characteristics of individual patients' immune responses. Thus, almost every antibody sample will vary from the reference

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material with respect to isotype/subclass (eg, IgM vs. IgG) and FVIII avidity, affinity, and epitope specificity. Therefore a reference sample and a clinical test sample are unlikely to exhibit parallel inhibition curves. The non-parallelism between the reference and test samples will result in high levels of error in most of the reported results, making the selection and adoption of an international reference sample a complicated solution to this problem.

Assay insensitivity was also reviewed, and there was a recommendation for the use of a low-titer inhibitor method to increase sensitivity. If available, Wyeth would like to review information on the assay performance characteristics (such as specificity, precision, linearity, ruggedness) of the modified assay. The method involves a concentration step, which is likely to affect assay precision and recovery of inhibitor activity, but no data on this were presented. As evidence of greater sensitivity of the modified assay, positive results were observed with 2 patients who had clinical evidence of inhibitors (altered PK) but were considered to be inhibitor-negative by the standard Nijmegen assay. Useful additional data would include results from inhibitor-negative individuals without clinical evidence of inhibitor to demonstrate specificity of the positive results.

Furthermore, following clinical interpretation of assay results, the rate of inhibitor development from single-arm safety and efficacy studies is normally compared to historical controls. Should more sensitive assays ultimately demonstrate value in detecting clinically relevant safety information, historical data in individual patients as well as in study populations will need to be generated with these more sensitive assays. Until such time, we will be required to use available historical data, generated with less sensitive assays, as a baseline for comparison, complicating the introduction of these more sensitive assays for use in clinical studies.

In summary, at the present time Wyeth does not believe that sufficient information is available to warrant any changes to current clinical practice for the detection of inhibitors. Wyeth would be willing to collaborate with regulatory authorities, experts, and reference laboratories on harmonizing inhibitor detection methods and exploring the potential for an international reference standard.

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### 3. Pharmacokinetic Trials

Wyeth agrees with FDA comments made during the workshop that comparative PK studies are required to support licensure of new rFVIII molecules. Wyeth also understands that on a case-by-case basis, comparative PK studies may be warranted for major changes to the manufacturing process. During the workshop, the FDA representative also stated that FDA now requires future new products to be tested for bioequivalence in a PK crossover study against a licensed plasma-derived FVIII product. The FDA noted that this was a new requirement, whereas in the past a comparison against the predecessor product had been acceptable. Several physician attendees with significant clinical experience in hemophilia care voiced strong disagreement with this proposal at the meeting, including representatives of Wyeth. Wyeth would like to reaffirm that we disagree with the FDA proposal that licensed plasma-derived FVIII products should be required as the comparative agent in PK studies.

A total of 5 rFVIII products have been approved: Recombinate, Kogenate, ReFacto, and Kogenate FS, following a PK crossover study against a plasma-derived FVIII, and Advate, following a PK crossover study against a rFVIII product, where bioequivalence was established in all cases. During the early development of recombinant products, the use of a plasma-derived comparator was appropriate due to the absence or limited availability of licensed rFVIII products when such PK studies were conducted. Following approval of the first rFVIII product by FDA and other regulatory authorities, there have been more than 10 years of post-marketing experience with recombinant products.

In the US, the Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation has recommended recombinant factor products for the treatment of hemophilia A and B because of their increased viral safety. Similar recommendations have been made by physician and advocacy groups as well as governments in Canada and many western European countries. As such, Wyeth believes it would be ethically and medically difficult to approach patients currently treated with recombinant products and ask them to agree to be infused with plasma-derived products for the purposes of a clinical study. With acknowledgement that the FDA regards all marketed products as safe, we point to the reluctance of the hemophilia community (both medical staff and patients) to expose hemophilia patients to any potential risk of infection after the contamination of blood products in the 1980s. Because more than 80% of hemophilia A patients in the US and

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more than 90% in Canada currently use rFVIII, and within the next 2 to 3 years all patients in the UK and most in France will likely do the same, it will be very difficult to recruit patients in studies that require the use of plasma-derived products.

In summary, Wyeth recommends that with the clinical and commercial success of Recombinate, Kogenate/Kogenate FS, and ReFacto, it seems scientifically sound and pragmatic to allow any licensed recombinant product to be used as a standard in a PK crossover study to establish bioequivalence of future products. This proposal would appear consistent with the recent action from the FDA in which Advate was licensed partially based on a PK crossover against Recombinate, where bioequivalence of these 2 rFVIII products was established. The recommended standard of care in the community is to use rFVIII, and Wyeth proposes that future rFVIII products should be measured against any one of the current standards.

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### **4. Safety Endpoints for Clinical Studies of Previously Treated Patients with Hemophilia A**

#### **4.1 Safety Assessment of Potentially Product-Related New Inhibitors in Hemophilia Study Patients**

There are multiple complexities associated with FVIII inhibitor formation, requiring careful clinical interpretation and assessment of each inhibitor case in order to determine the clinical importance of each case. To determine if inhibitor formation in a particular study patient corresponds to an important safety signal of a product's neoantigenicity, clinical judgment is required. One must carefully consider an individual patient's underlying inhibitor risk, based on FVIII genotype, other genetic confounding factors such as HLA type, family history, environmental factors, comorbid diseases that may predispose to immune responses, or past personal history of inhibitor. Therefore, Wyeth believes that due to these complexities, it is most appropriate that safety assessments for predicting neoantigenicity of new FVIII products in clinical studies on PTPs be restricted to patients who specifically develop de novo inhibitors, distinguishing these events from inhibitors in other patients with previous inhibitor(s), even at low titer, who are not well suited for determination of a product's neoantigenicity. Other factors important to assessing a safety signal in addition to the aforementioned risk factors are the responsiveness of the inhibitor to subsequent therapy and the patient's clinical outcome.

Historically, single-arm safety and efficacy studies with an objective to determine the observed incidence of inhibitor development have been a pre-licensure requirement for rFVIII molecules. Individual prospective studies for regulatory approval have not been designed to accurately identify the true population rate of inhibitors, following use of a specific FVIII product, or statistically significant differences between the observed rate of inhibitor development in a study group and a true rate of inhibitor development in the population. The studies have primarily been designed such that any "cluster" effect on increased incidence of inhibitor development associated with a manufacturing change or new product would be identified as a distinctly different clinical outcome compared with historical experience using similar FVIII preparations. One example of a clinically important cluster of inhibitors generally acknowledged to be truly product related is noted in the Belgian and Dutch experience in the late 1990s following the introduction of a double virus-inactivated FVIII product using solvent-detergent and pasteurization methods.<sup>1,2</sup>

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Therefore, any proposed guideline or requirement for the formal assessment of the incidence of inhibitor development for new or modified rFVIII products should incorporate the following components. Firstly, acknowledgement that safety assessments for predicting neoantigenicity should be restricted to de novo inhibitors. Secondly, if statistical guidelines are to be established, they must be able to differentiate between the observation of a random event(s) such as the occurrence of inhibitors in PTPs consistent with historical data and a truly product-related event associated with causing an antigenic response.

### 4.2 Historical Data

As Wyeth stated at the meeting, the safety of approved products provides important reference in establishing the standards for future products. The published literature that describes the inhibitor experience in the pivotal trials for all rFVIII products is revealing. These data for each product are summarized below.

- Kogenate: first generation full-length (FL) rFVIII (Schwartz et al., *NEJM* 1990)<sup>3</sup>

High-titer inhibitors developed in 2 of 86 PTPs (2.3%; CI=0.28–8.15). In 1 of these inhibitor patients, Western blot analysis of baseline samples detected antibody to FVIII. Hence the investigators reported, “De novo formation of inhibitors occurred in only 1 of 85 previously treated subjects.”<sup>3</sup>

- Recombinate: first generation FL rFVIII (White et al., *Thromb Haemost* 1997)<sup>4</sup>

Inhibitors developed in 2 of 69 PTPs (2.9%; CI=0.35–10.08). One (1) patient had a history of a previous low-titer inhibitor, and 1 patient had a low-titer inhibitor at baseline that became a high-titer inhibitor. Hence, the investigators reported, “No patient developed an inhibitor to rFVIII.”<sup>4</sup>

- Kogenate FS: second generation FL rFVIII (Abshire et al., *Thromb Haemost* 2000)<sup>5</sup>

Inhibitor developed in 1 of 71 PTPs (1.4%; CI=0.04–7.60). This patient had a low-titer inhibitor (0.39 BU) prior to study entry and was considered to have developed a recurrent inhibitor based on this prior history. Hence, the investigators reported, “No evidence of de novo inhibitor formation was observed.”<sup>5</sup>

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- ReFacto: second generation B-domain deleted (BDD) rFVIII (Courter and Bedrosian, *Sem Hematol* 2001)<sup>6</sup>

Inhibitor developed in 1 of 113 PTPs (0.9%; CI=0.02–4.83), which was a de novo inhibitor, as described.

- Advate: third generation FL rFVIII (FDA Summary of Basis for Approval, STN 125063/0)<sup>7</sup>

Inhibitor developed in 1 of 103 PTPs (1%; CI=0.02–5.4).

The distinction in several of these articles between the reports of all inhibitors in all patients and reports of inhibitors considered to be clinically important for assessment of neoantigenicity demonstrates a longstanding history of applying clinical judgment to the analysis of inhibitor formation to assess neoantigenicity of new rFVIII products.

### 4.3 Comments on FDA Proposed Statistical Approach

The FDA has proposed a statistical standard for clinical trials of new FVIII products with respect to acceptable inhibitor incidence. It is proposed that this new standard be adopted for safety evaluation of the neoantigenicity of FVIII products. Such studies are typically undertaken in PTPs with severe hemophilia A. Specifically, FDA has stated that for the trial to be successful, the upper bound of the 2-sided 95% confidence interval for the product incidence rate must be below 6.8%, and the calculation is to be based on an intent-to-treat paradigm. The implications of this standard are illustrated in Table 1 below.

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TABLE 1. IMPLICATIONS OF THE PROPOSED FDA MODEL REQUIRING THE UPPER LIMIT OF THE 2-SIDED 95% CONFIDENCE INTERVAL FOR INHIBITOR FORMATION TO BE <6.8%

True population incidence of inhibitors	Probability of achieving $\leq 1$ inhibitor in 80 patients	Sample size (N) needed to have 80% probability that the sample proportion of inhibitors is such that the upper bound of the 2-sided 95% confidence interval is <6.8%	Maximum number of inhibitors that could be observed
1%	0.81	—	—
2%	0.52	148	4/148
3%	0.30	247	9/247
4%	0.17	537	25/537
5%	0.09	1391	76/1391
6%	0.04	7678	478/7678
6.5%	0.03	53526	3526/53526

Source: Computed using NCSS 2004, Number Cruncher Statistical Systems.

The second column of the table illustrates the statistical power of a study of 80 patients to achieve the stated goal, because only a finding of  $\leq 1$  inhibitor in 80 patients would achieve the FDA requirement. Unless the true population incidence of inhibitors with a specific product is less than or equal to 1%, the power of such a trial would be unacceptable by the usual minimum standards demanding at least 80% power. As revealed at the workshop, clinical experts could not provide a consensus on what the true population rate is, and furthermore, the Canadian population survey data<sup>8</sup> that were updated at the meeting indicated that the true rate may be in the 3% range.

Despite the lack of consensus, the proposed standard is a de facto requirement that a new FVIII product have no worse than a 1% true population inhibitor rate to have a reasonable chance of being successful in the trial. This presumes that a study of 80 patients be conducted. Eighty (80) is a typical sample size, partly based on regulatory guidances in the development of these studies and partly based on long-standing acceptance of what can reasonably be accomplished in a rare disease setting. Of course, it may be argued theoretically that a larger sample size could be incorporated into the study design in order to achieve the same goal by increasing the power of the study. The third column of the table shows the necessary sample size to obtain 80% power for larger, but potentially reasonable, population inhibitor incidence rates. For 2% true inhibitor incidence, a sample of 148 patients would be needed. Beyond this rate, samples of about 250 or more patients are needed. These are sizes far beyond that which any study of neoantigenicity in PTPs with

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severe hemophilia A has undertaken to date, and the need to increase study size to this degree will have a negative impact on the development of new products. Furthermore, it may be argued that these numbers are beyond the realm of possibility given the rarity of this orphan disease, the small size of the patient population available for such studies who would meet inclusion criteria, the number of studies ongoing, and the organizational difficulties, complexity, and extreme expense of such studies. Thus, using the upper bound of a 2-sided confidence interval as a criterion is not well suited to define a safety threshold for inhibitors, a low-incidence safety signal, in small study patient populations such as PTPs with severe hemophilia.

The new FDA standard, as proposed, precludes the study of any product whose incidence rate for inhibitors might be expected to be any larger than about 1%. So, although the standard requires that the upper bound of the 95% confidence interval be less than 6.8%, essentially it demands that products meet a much stricter population requirement. The inherent problem with applying 6.8% as a fixed metric for determining a safety endpoint threshold is that the upper bound of the confidence interval is a random variable that reflects the particular sample group studied. It is not a population parameter. Furthermore, the FDA proposal calls for a study analysis using an intent-to-treat principle, applying a quantitative metric based on all observed inhibitors as a safety endpoint, without due consideration of the clinical context of inhibitor formation.

Thus the FDA proposal described, if applied to the currently available rFVIII replacement products, would have unduly precluded licensing of Kogenate, Recombinate, and Kogenate FS, because each of these products had observed inhibitor incidence rates based on intent-to-treat analysis, whose upper bound of the 95% 2-sided confidence interval exceeded 6.8% (see Section 4.2). If the belief of the FDA is that products whose population inhibitor rates are <6.8% are acceptable, then a statistical method that allows for acceptance of such products under reasonably designed studies must be incorporated into an alternative analytical approach.

### **4.4 Alternative Statistical Proposal**

Wyeth suggests the use of Bayesian analysis<sup>9</sup> as an alternative appropriate to the analysis of a low-incidence adverse event (eg, inhibitor development) in relatively small clinical studies. Basically, if an upper bound on a population rate can be agreed to, and a probability

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of achieving that goal is set, say 90% for instance, then a Bayesian approach would provide the evidence needed.

Bayesian analysis requires that we assume that the distribution of the number of inhibitors, given a particular inhibitor rate, is binomial ( $X; n, p$ ), where  $n$  is the sample size and  $p$  is the assumed inhibitor rate. Furthermore, we assume that the prior distribution of the inhibitor rate has a beta distribution that reflects a prior belief that this rate is likely to be relatively small and very unlikely to be very large. Parameters  $\alpha = 0.1$  and  $\beta = 3.9$ , for instance, adequately describe such a distribution for rates of inhibitor development with a mean of 2.5% ( $\alpha/[\alpha+\beta]$ ), which is in line with data from large population surveys of inhibitor incidence in PTPs with hemophilia A, which reported rates up to 3.0% and 3.2%, respectively (Giles et al.<sup>8</sup> and McMillan et al.<sup>10</sup>). Then the posterior distribution of the inhibitor rate, given the data generated in a study, is also beta with parameters  $\alpha+x$  and  $\beta+n-x$ .

TABLE 2. BAYESIAN POSTERIOR PROBABILITIES FOR SCENARIOS IN STUDIES WITH 80 OR 100 PATIENTS

Upper threshold value for true population incidence of inhibitors	80 Patients			100 Patients		
	Posterior probability that the true population incidence of inhibitors is less than the corresponding upper threshold value	Posterior probability that the true population incidence of inhibitors is less than the corresponding upper threshold value	Posterior probability that the true population incidence of inhibitors is less than the corresponding upper threshold value	Posterior probability that the true population incidence of inhibitors is less than the corresponding upper threshold value	Posterior probability that the true population incidence of inhibitors is less than the corresponding upper threshold value	Posterior probability that the true population incidence of inhibitors is less than the corresponding upper threshold value
	If 1 inhibitor observed in 80 patients	If 2 inhibitors observed in 80 patients	If 3 inhibitors observed in 80 patients	If 1 inhibitor observed in 100 patients	If 2 inhibitors observed in 100 patients	If 3 inhibitors observed in 100 patients
1%	0.52	0.18	0.04	0.60	0.25	0.07
2%	0.78	0.47	0.21	0.85	0.58	0.32
3%	0.90	0.69	0.43	0.95	0.80	0.58
4%	0.96	0.83	0.63	0.98	0.91	0.77
5%	0.98	0.91	0.77	0.99	0.96	0.88
6%	0.99	0.96	0.87	1.00	0.98	0.94
6.8%	1.0	0.98	0.92	1.00	0.99	0.97

Source: Posterior probabilities were computed using SAS version 8.2 on UNIX with a prior distribution of beta (0.1, 3.9).

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Table 2 provides the posterior probability that the true incidence of inhibitors is less than some given upper threshold value for different possible scenarios in an 80- or 100-patient study. Thus, in a study with 1 inhibitor out of 80, the results support with 90% probability that the population inhibitor rate may only be as high as 3%, while 2 inhibitors out of 80 support rates up to just less than 5% with 90% probability. By adopting the acceptable maximum population inhibitor formation rate put forth by the FDA of 6.8% as the upper threshold value and agreeing on an acceptable posterior probability, for instance 90% as proposed in this example, then reasonable conclusions may be drawn.

Before adopting a Bayesian model as proposed above, one must test this approach against known data to see if the model works appropriately. Consider the following data presented in Table 3 for all approved rFVIII products and for a plasma-derived FVIII that caused a sudden increase in FVIII inhibitors in PTPs with hemophilia A in Belgium<sup>1</sup> and the Netherlands<sup>2</sup>, hereafter referred to as the Bisinact experience.

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TABLE 3. BAYESIAN POSTERIOR PROBABILITIES FOR THE PREVIOUSLY REPORTED CLINICAL STUDIES OF INHIBITOR DEVELOPMENT IN APPROVED rFVIII PRODUCTS AND IN THE BELGIAN INHIBITOR OUTBREAK

Upper threshold of true population incidence of inhibitors	Posterior Probability					
	Observe 2/86 (2.3%) Kogenate	Observe 2/69 (2.9%) Recombinate	Observe 1/71 (1.4%) Kogenate FS	Observe 1/113 (0.9%) ReFacto	Observe 1/103 (1.0%) Advate	Observe 8/140 (5.7%) Bisinact
1%	0.20	0.14	0.48	0.65	0.61	0.00
2%	0.50	0.39	0.74	0.89	0.86	0.01
3%	0.73	0.61	0.88	0.96	0.95	0.06
4%	0.86	0.77	0.94	0.99	0.98	0.20
5%	0.93	0.87	0.97	1.00	0.99	0.41
6%	0.97	0.93	0.99	1.00	1.00	0.62
6.8%	0.98	0.95	0.99	1.00	1.00	0.75

Source: Posterior probabilities were computed using SAS version 8.2 on UNIX with a prior distribution of beta (0.1, 3.9).

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The proposed FDA standard requires that a study demonstrate a true population inhibitor rate less than 6.8%. Using the proposed Bayesian statistical model, inspection of clinical data in Table 3 indicates that all products currently approved for use in the US would meet the stringency of such a requirement with a high probability of 90% or greater. The data in Table 3 indicate that the Kogenate study supported a rate of up to 5% with at least 90% probability. Similarly, the Recombinate study supported a rate of up to 6%; the Kogenate FS study supported a rate of up to 4%; and the ReFacto and Advate studies supported rates of up to 3% with at least 90% probability. In contrast, the Bisinact experience indicated that there was only a 75% probability that the true population inhibitor incidence rate was less than 6.8%. Because it was less than 90% probable that the true rate was lower than 6.8%, Bisinact would not have met the criteria for product approval by this proposed Bayesian statistical model.

Thus, we urge the FDA to consider revising its approach. Wyeth recommends that the Bayesian model described above to evaluate the safety of the currently approved rFVIII products be adapted for the licensure of future products, rather than the confidence-interval approach as proposed by the FDA. Wyeth believes this alternative statistical strategy will promote the continued development of new products by providing rigorous assessment around reasonably sized studies for this patient population.

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### **5. Summary**

In conclusion, Wyeth has provided feedback highlighting some of the complexities affecting assay performance and the limitations of data that were presented to support more sensitive inhibitor assays and their use. At this time insufficient information is available to recommend revising current standard assay procedures for use of the classic Bethesda assay and Nijmegen modification in clinical studies.

Wyeth also reaffirms comments made at the workshop indicating that any licensed rFVIII product provides an appropriate control for comparative PK studies of new or modified rFVIII products. Wyeth believes the FDA recommendation to require future PK studies compare against a plasma-derived FVIII product is contrary to US National Hemophilia Foundation guidelines and may not be possible in countries such as the USA, Canada, and many European countries where the majority of patients currently receive rFVIII products as the standard of care.

Wyeth believes that clinical interpretation of inhibitor development should be central to future guidance for clinical trials. The recommendation by FDA is to establish a statistical standard for clinical trials of new FVIII products wherein the upper bound of the 2-sided 95% confidence interval for the product inhibitor incidence rate must be below 6.8%, and the calculation is to be based on an intent-to-treat paradigm. Wyeth does not agree with this approach as it relies on an estimate of the true rate of inhibitor incidence to be less than or equal to 1%. At the workshop, clinical experts did not agree with this point estimate as they felt this was too low. Additionally, many of the successful commercial products would not be able to meet the FDA proposal. In response, Wyeth has recommended an alternate statistical approach based on Bayesian analysis.

Wyeth has provided analysis indicating that the Bayesian approach has the sensitivity to discriminate between rFVIII products that are licensed and Bisinact, where a manufacturing process change was associated with a higher rate of inhibitor development. Wyeth believes this statistical approach is well suited to evaluate a low-incidence safety endpoint such as inhibitor development in PTPs in the context of a small-sized study, which is feasible in PTPs with severe hemophilia A.

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